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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)

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☐ Additional inventors are being named on the _____ separately numbered sheets attached hereto

TITLE OF THE INVENTION (500 characters max)

Method for Treating Nausea and Vomiting in Pregnancy

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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification Number of Pages 9
☒ Drawing(s) Number of Sheets 1
☐ Application Data Sheet. See 37 CFR 1.76
☐ CD(s), Number
☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☑ Applicant claims small entity status. See 37 CFR 1.27.
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Respectfully submitted,

SIGNATURE [signature] Date 7.18.03

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4249

Method for Treating Nausea and Vomiting

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U.S. PATENT DOCUMENTS

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Abstract:

A method is disclosed for treating nausea and vomiting by stimulation, comprising attaching one or more electrodes or wires on or under the skin of the neck, near the vagus nerve fibers in the neck; attaching these electrodes or wires to a current source; and stimulating the vagus nerve by means of this current source. The electrodes or wires can be directly attached to the current source by electrical wiring. Alternatively, they could remain under the skin or muscles of the neck with stimulation delivered from the current source to the electrodes and their associated electronics by means of induction. As a further alternative, they could be placed over the abdomen, or beneath the abdominal wall, in or near the gastrointestinal tract, or in or near the vagus nerve fibers in the vicinity of the stomach or esophagus. The current source can be adjusted with respect to milliamperes of current, duration of pulse, duration of pulse train, and frequency of pulse or pulse train repetition. Optionally, stimulation could be performed using a magnetic stimulator with the output pulse adjustable with respect to joules, duration of pulse, number of pulses, duration of pulse train, and frequency of pulse train. The device may be designed so that it would turn on manually. Alternatively, it may be designed so that it would turn on at designated times, turn off at designated times, or both. Provisions are made for the device to be connected to one or more sensors measuring gastic motility, heart rate, respiratory rate, skin resistance, brain activity, or other measures, with the pulses activated based on the activity measured by the sensors.

Other Publications:

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Zabara JCRBJrTMF. Neuroinhibition in the Regulation of Emesis. Space Life Sciences 1972; 282-292.

Claims:

What is claimed is:

1. A method for treating nausea and vomiting comprising the steps of:

placing on, or attaching on or under the skin of the neck one or more electrodes;

attaching said electrodes to a current source, said current source powered by batteries or by standard commercial electrical current, and said current source adjustable with respect to milliamperes of current, duration of pulse, duration of pulse train, and frequency of pulse or pulse train repetition;

passing current from said current source to said electrodes;

whereby the vagus nerve in the neck can be stimulated, thereby reducing nausea and vomiting.

2. A method according to claim 1, whereby said electrodes are attached under the skin of the neck and current is delivered from said current source to said electrodes and their associated electronics by means of induction, rather than by direct attachment.

3. A method for treating nausea and vomiting by delivering a magnetic pulse from a magnetic stimulator, said stimulator adjustable with respect to joules, duration of pulse, number of pulses, duration of pulse train, and frequency of pulse or pulse train repetition;

whereby the vagus nerve in the neck can be stimulated, thereby reducing nausea and vomiting.

4. A method for treating nausea and vomiting comprising the steps of:

placing on, or attaching on or under the skin of the abdomen one or more electrodes, said means of stimulation selected from the group comprising electrodes or wires;

attaching said electrodes, said current source powered by batteries or by standard commercial electrode current, and said current source adjustable with respect to milliamperes of current, duration of pulse, duration of pulse train, and frequency of pulse or pulse train repetition;

passing current from said current source to said electrodes;

whereby the vagus nerve can be stimulated, thereby reducing nausea and vomiting.

5. A method for treating nausea and vomiting comprising the steps of:

attaching in the vicinity of an organ selected from the group comprising the stomach and esophagus one or more electrodes;

attaching said electrodes to a current source, said current source powered by batteries or by standard commercial electrode current, and said current source adjustable with respect to milliamperes of current, duration of pulse, duration of pulse train, and frequency of pulse or pulse train repetition;

passing current from said current source to said electrodes;

whereby the vagus nerve can be stimulated, thereby reducing nausea and vomiting.

6. A method according to claims 1-5 whereby stimulation is turned on manually.

7. A method according to claims 1-5 whereby stimulation is turned on automatically at predesignated times.

8. A method according to claims 1-5 whereby stimulation is turned off automatically at predesignated times.

9. A method according to claims 1-5 whereby stimulation is turned off automatically at predesignated times and off at predesignated times.

10. A method according to claims 1-5 whereby stimulation is turned on in response to one or more sensors, said sensors selected from the group comprising sensors measuring gastric motility, heart rate, respiratory rate, skin resistance, brain activity.

11. A method according to claims 1-10 in which the disorder treated is nausea or vomiting of pregnancy.

12. A method according to claims 1-10 in which the disorder treated is nausea or vomiting due to chemotherapy for cancer.

13. A method according to claims 1-10 in which the disorder treated is nausea or vomiting due to chemotherapy for inflammatory diseases of the body.

14. A method according to claims 1-10 in which the disorder treated is nausea or vomiting due to chemotherapy for connective tissue diseases of the body.

15. A method according to claims 1-10 in which the disorder treated is nausea or vomiting due to chemotherapy for f inflammatory or autoimmune disorders of the peripheral or central nervous system

16. A method according to claims 1-10 in which the disorder treated is nausea or vomiting due to post-operative nausea.

18. A method according to claims 1-10 in which the disorder treated is nausea or vomiting due to motion sickness.

BACKGROUND OF THE INVENTION

1. Field of the invention
The invention pertains to an acute method of treating nausea and vomiting, by means of stimulation of the vagus nerve.

2. Description of Related Art.

Nausea and vomiting is a significant problem during pregnancy, especially during early pregnancy. The problem is generally estimated to affect about 70-80% of women.[Parsonnet *et al.* 1966] [Broussard and Richter 1998a] [Gadsby *et al.* 1993] [Jarnfelt-Samsioe *et al.* 1983] [Klebanoff *et al.* 1985;Nageotte *et al.* 1996b] [Safari *et al.* 1998] [Snell *et al.* 1998]

This is especially a problem during early pregnancy, but can be present throughout pregnancy in about 20% of pregnant women.[Broussard and Richter 1998c] In a smaller number of pregnant women (about 0.3-2%0, this is severe enough to cause significant dehydration, disturbed electrolyte balance, weight loss, and ketosis, called hyperemesis gravidarum. ([Abell and Riely 1992] [Broussard and Richter 1998b;Depue *et al.* 1987] [Fairweather 1968] [Hod *et al.* 1994;Kallen 1987;Nageotte *et al.* 1996a] Admission to the hospital may be necessary.

Medications for emesis are available, but none are universally effective. Moreover, medications carry a risk of fetal malformations and their use is discouraged.[Broussard and Richter 1998d] Although, fluids, electrolytes and general nutrition can be replenished to the pregnant woman, nausea and vomiting cause considerable discomfort to the pregnant woman, and no ideal treatment is available. It is well known that the gastrointestinal tract is innervated by the vagus nerve [Schachter and Saper 1998;Zabara *et al.* 1972;Zabara 1988] and it has been shown that stimulation of vagal fibers can suppress experimental vomiting.[Zabara, Chaffee, Jr., and Tansy1972;Zabara1988] Therefore, stimulation of these fibers could be a means of treating nausea and vomiting of pregnancy.

This is not the only setting in which nausea and vomiting is a serious problem. Chemotherapy for cancer or for severe forms of connective tissue diseases or inflammatory diseases of the body, or chemotherarpy for inflammatory or autoimmune disorders of the peripheral or central nervous system, can require use of agents that produce nausea, vomiting, or both. Examples of.connective tissue diseases or inflammatory diseases of the body comprise disorders such as lupus erythematosus, rheumatoid arthritis, scleroderma, dermatomysitis, ulcerative colitis. Examples of inflammatory or autoimmune disorders of the peripheral nerves or central nervous system comprise disorders such as chronic inflammatory demyelinating polyneuropathy, multiple sclerosis, neruosarcoidosis, central nervous system lupus, central nervous system vasculitis, monoclonal gammopathy. Finally, some patients experience severe motion sickness. Moreover, the disorders listed above can themselves cause nausea or vomiting. There are medications available for treating these situations. None of these are universally effective, however.

Bertolucci '91 (US Patent # 4,981,146) discloses treatment of nausea and vomiting by use of electrical stimulation of the wrist, in the region of the median nerve, at the P6 accupuncture point. This treatment has become commercially available with an FDA approved device (ReliefBand, http://www.woodsidebiomedical.com). This treatment has shown some benefit. However, as the company itself acknnowedges on its web site (http://www.woodsidebiomedical.com/scientific_evidence.asp) this treatment is not universally or completely effective. The efficacy found supports, however, the idea that stimulation could be an effective means of treating nausea and vomiting. The vagus nerve more directly connects to the central nervous system and is known to connect to centers pertinent to vomiting. Therefore, stimulation of the vagus nerve could more directly, and more effectively, treat nausea and vomiting.

Therefore, a need exists to improve the treatment of nausea and vomiting, a problem that affects a significant proportion of the population.

SUMMARY OF THE INVENTION

An object of the invention provides for the use of vagal nerve stimulation for treating nausea and vomiting comprising the steps of:

attaching on or under the skin of the neck one or more electrodes;

attaching said electrodes to a current source, said current source powered by batteries or by standard commercial electrode current, and said current source adjustable with respect to milliamperes of current, duration of pulse, duration of pulse train, and frequency of pulse or pulse train repetition;

passing current from said current source to said electrodes;
whereby the vagus nerve in the neck can be stimulated, thereby reducing nausea and vomiting due to disorders selected from a list comprising pregnancy, chemotherapy for cancer, chemotherapy for inflammatory diseases of the body, chemotherapy for connective tissue diseases of the body, chemotherapy for inflammatory or autoimmune disorders of the peripheral or central nervous system, cancer, inflammatory or connective tissue disease, inflammatory disease of the body, inflammatory or autoimmune disorders of the peripheral or central nervous system, post-operative nausea, or motion sickness.

A further object of the invention provides for the use of vagal nerve stimulation for treating nausea and vomiting comprising the steps of:
attaching under the skin of the neck one or more electrodes;
utilizing a current source, said current source powered by batteries or by standard commercial electrode current, and said current source adjustable with respect to milliamperes of current, duration of pulse, duration of pulse train, and frequency of pulse or pulse train repetition;
passing current from said current source to said electrodes and their associated electronics by means of induction;
whereby the vagus nerve in the neck can be stimulated, thereby reducing nausea and vomiting due to disorders selected from a list comprising pregnancy, chemotherapy for cancer, chemotherapy for inflammatory diseases of the body, chemotherapy for connective tissue diseases of the body, chemotherapy for inflammatory or autoimmune disorders of the peripheral or central nervous system, cancer, inflammatory or connective tissue disease, inflammatory disease of the body, inflammatory or autoimmune disorders of the peripheral or central nervous system, post-operative nausea, or motion sickness.

A further object of the invention provides for the use of vagal nerve stimulation for treating nausea and vomiting by delivering a magnetic pulse from a magnetic stimulator, said stimulator adjustable with respect to joules, duration of pulse, number of pulses, duration of pulse train, and frequency of pulse or pulse train repetition;
whereby the vagus nerve in the neck can be stimulated, thereby reducing nausea and vomiting due to disorders selected from a list comprising pregnancy, chemotherapy for cancer, chemotherapy for inflammatory diseases of the body, chemotherapy for connective tissue diseases of the body, chemotherapy for inflammatory or autoimmune disorders of the peripheral or central nervous system, cancer, inflammatory or connective tissue disease, inflammatory disease of the body, inflammatory or autoimmune disorders of the peripheral or central nervous system, post-operative nausea, or motion sickness.

A further object of the invention provides for the use of vagal nerve stimulation for treating nausea and vomiting comprising the steps of:
attaching on or under the skin of the abdomen one or more electrodes;
attaching said electrodes to a current source, said current source powered by batteries or by standard commercial electrode current, and said current source adjustable with respect to milliamperes of current, duration of pulse, duration of pulse train, and frequency of pulse or pulse train repetition;
passing current from said current source to said electrodes;
whereby the vagus nerve in the neck can be stimulated, thereby reducing nausea and vomiting due to disorders selected from a list comprising pregnancy, chemotherapy for cancer, chemotherapy for inflammatory diseases of the body, chemotherapy for connective tissue diseases of the body, chemotherapy for inflammatory or autoimmune disorders of the peripheral or central nervous system, cancer, inflammatory or connective tissue disease, inflammatory disease of the body, inflammatory or autoimmune disorders of the peripheral or central nervous system, post-operative nausea, or motion sickness.

A further object of the invention provides for the use of vagal nerve stimulation for treating nausea and vomiting comprising the steps of:
attaching in the vicinity of an organ selected from the group comprising the stomach and esophagus one or more electrodes;
attaching said electrodes to a current source, said current source powered by batteries or by standard commercial electrode current, and said current source adjustable with respect to milliamperes of current, duration of pulse, duration of pulse train, and frequency of pulse or pulse train repetition;
passing current from said current source to the means of stimulation;

whereby the vagus nerve can be stimulated, thereby reducing nausea and vomiting due to disorders selected whereby the vagus nerve in the neck can be stimulated, thereby reducing nausea and vomiting due to disorders selected from a list comprising pregnancy, chemotherapy for cancer, chemotherapy for inflammatory diseases of the body, chemotherapy for connective tissue diseases of the body, chemotherapy for inflammatory or autoimmune disorders of the peripheral or central nervous system, cancer, inflammatory or connective tissue disease, inflammatory disease of the body, inflammatory or autoimmune disorders of the peripheral or central nervous system, post-operative nausea, or motion sickness.

The invention provides for the turning on stimulation either manually or automatically at predesignated times. The invention also provides a possibility for turning off stimulation automatically at predesignated times. The invention also provides for turning on stimulation in response to one or more sensors, said sensors selected from the group comprising sensors measuring gastric motility, heart rate, respiratory rate, skin resistance, brain activity.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the main components of the invention. Electrodes are placed on the skin or within the neck. A stimulation device is used to determine the stimulation parameters, which are then delivered through the electrodes.

DESCRIPTION OF PREFERRED EMBODIMENT

An embodiment of the invention relates to stimulation of the vagus nerve as a treatment for nausea and vomiting. The vagus nerve is a mixed nerve, and a primary function of this nerve is to innervate the heart, lungs, and gastrointestinal system. The right vagus nerve innervates the atria of the heart, the left the ventricles. The vagus nerve in the neck travels beneath the sternocleidomastoid muscle, and is about an inch below the skin surface. Fibers to the ventricles are less plentiful, so stimulation of the left vagus nerve is less likely to disrupt cardiac rhythm. Fibers from the left vagus nerve travel via the ventral surface of the esophagus, through the diaphragm, and then primarily to the anterior surface of the stomach.

Nausea and vomiting may be treated by stimulation of the vagus nerve. Stimulation could be performed as a single pulse, or as a train of pulses and the characteristics of the pulses including pulse amplitude (measured in amperes or joules), pulse duration, pulse train duration, and frequency of pulse or pulse train repetition. Stimulation could be accomplished by placing the stimulating electrodes directly on the neck, or by attaching electrodes to the neck. It is well known that electrodes can be attached easily in a number of ways. To give examples, each electrode could be attached to an adhesive substance, or the electrodes themselves could be attached with paste or collodion, or the electrodes could be in the shape of a needle and placed under the skin. In a preferred embodiment, the electrodes would be on the left side of the neck, over the vagus nerve, so as to stimulate the left vagus nerve.

Alternately, the electrodes could be placed under the skin, with no direct "wired" connection to the outside. These could be directly under the skin, or deeper, below the sternocleidomastoid muscle, so as to be closer to the vagus nerve. Stimulation would be delivered to the electrodes and their associated electronics by means of induction through the skin.

Alternately, stimulation electrodes could held in place on the skin of the abdomen, or affixed by the adhesive means described above, or placed under the skin, or deeper, near the vagus nerve fibers that are in the vicinity of the stomach.

The electrodes could be in a variety of shapes including discs or wires, according to the invention. The current source either would be connected directly to the electrodes by means of wires or else current would be delivered through the skin to the electrodes and their associated electronics by means of induction. Electrodes could be reusable or disposable, according to the invention.

Alternatively, stimulation of the vagus nerve could be accomplished by magnetic stimulation. It is well known that magnetic stimulation can be focused, so that the effects of stimulation could be localized to a

specific region for which activation is desired. Since the nerve could be in a different location in different people, two- or three-dimensional imaging (i.e. magnetic resonance imaging or computerized tomography) could be used to precisely locate the target nerve region and localize this region with respect to specific locations on the skin surface.

The invention is envisioned as a means of controlling nausea and vomiting when it occurs, by stimulating the vagus nerve, thus reducing the nausea and vomiting. The effectiveness of vagus nerve stimulation for this purpose has been shown experimentally.[Zabara 1972;Zabara1988] Direct vagus nerve stimulation is used clinically for treatment of intractable seizures of partial onset. (see Zabara '254, Zabara '164, Zabara '807) and this use is approved by the United States Food and Drug Administration (FDA) The approved device is placed surgically within the neck, in direct proximity to the nerve. Because of this, there is considerable experience regarding the possibility of adverse effects due to direct stimulation of the vagus nerve. This experience indicates that stimulation primarily causes effects localized to the area of stimulation. Common symptoms are hoarseness, throat pain, coughing, and dyspnea, paresthesias, and muscle pain, occurring at the time of stimulation. Importantly, there is no evidence to suggest that vagus nerve stimulation causes effects elsewhere in the body or causes birth defects. [Ben-Menachem *et al.* 1998]

Vagus nerve stimulation has been envisioned as a treatment for disorders other than epilepsy, including psychiatric disorders. Stimulation of other cranial nerves has been envisioned for treating a variety of neurological disorders including voluntary and involuntary disorders, migraine, epileptic seizure, motor disorders, Parkinson's disease, cerebral palsy, spasticity, chronic nervous illnesses and involuntary movement; pancreatic endocrine disorders including diabetes and hypoglycemia; dementia including cortical, subcortical, multi-infarct, Alzheimer's disease and Pick's disease; sleep disorders including central sleep apnea, insomnia and hypersomnia; eating disorders including anorexia nervosa, bulimia and compulsive overeating; and neuropsychiatric disorders including schizophrenia, depression and borderline personality disorder. (Zabara '569, Zabara '734)

Vagus nerve stimulation also has been envisioned for treating heart disorders (Zabara '282), hypertension (Terry '400, endocrine disorders such as diabetes and hypoglycemia (Wernicke '988). It also has been envisioned to treat gastric motility disorders such as duodenal ulcers, irritable colon, diverticulosis, and dumping syndrome. (Terry '730) Terry '730 however did not envision the use of vagus nerve stimulation for the innovative purposes envisioned in this disclosure.

Electrical stimulation is provided by two electrodes 1,2 placed on the vagus nerve. These are connected by a wire 3 to an implanted electronics package 4 that is also connected by a second wire 6 to an inductive pickup coil 6. The electronics package 4, wire 5, and pickup coil 6 are surgically place in a convenient body cavity away from the patient's neck where the vagal nerve stimulation is delivered.

The electronics package derives its power from an external inductive loop transmitter 7 that is placed over the implanted pickup coil 6. All control information is also transmitted by this magnetic inductive link. The inductive loop transmitter 7 is connected by a cable 8 to the external stimulation electronics and power supply 9. The external stimulation electronics 9 delivers either periodic or continuous stimulation at the desired level either under program control or on demand by the patient pressing a button 10.

An alternative embodiment of the invention uses electrodes placed on the skin surface . Two electrodes 11, 12 deliver electrical stimulation and are connected by a cable 13 to the alternative external stimulator electronics 14. A patient push button 15 is also provided to allow for on demand stimulation, as well as programmed continuous or periodic stimulation.

Still another alternative embodiment envisions placing the electrodes on the skin of the abdomen or within the abdomen. Still another alternative embodiment envisions stimulation using a magnetic coil.

Still another alternative embodiment envisions using batteries within the device.

Still another alternative embodiment envisions powering the device using ordinary commercial alternating current.

Still another alternative embodiment envisions powering the device using magnetic stimulation.

While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to those of ordinary skill in the art that various changes and modifications can be made therein without departing from the spirit and scope of the invention.

The content of all books, journal articles, abstracts and the like cited herein are hereby incorporated herein by reference.

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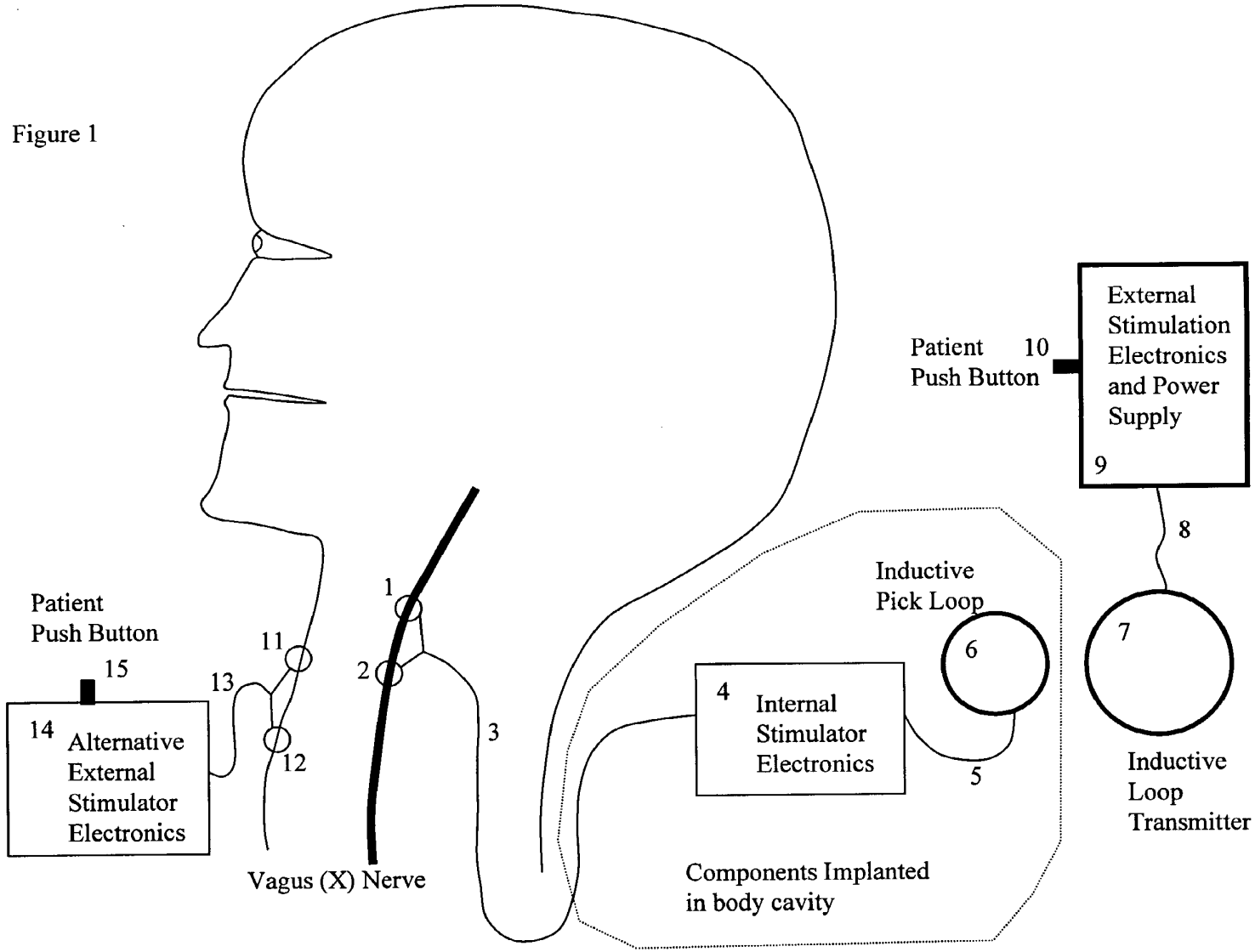
Figure 1


Patient
Push Button
10
External
Stimulation
Electronics
and Power
Supply
9
8
Inductive
Pick Loop
6
7
Inductive
Loop
Transmitter
1
2
3
4
Internal
Stimulator
Electronics
5
Components Implanted
in body cavity
Patient
Push Button
15
11
13
14
Alternative
External
Stimulator
Electronics
12
Vagus (X) Nerve